International Journal of Pharmaceutics 471 (2014) 322–331

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Design of transparent film-forming hydrogels of tolterodine and their effects on stratum corneum

Ximing Liu, Lu Fu, Wenwen Dai, Wei Liu, Jinlong Zhao, Yi Wu, Lengsheng Teng, Fengying Sun, Youxin Li *

Room 352, Life Sciences Building, School of Life Sciences, Jilin University, Qianjin Street No.2699, Changchun, Jilin 130012, China

ARTICLE INFO

Article history:
Received 24 February 2014
Received in revised form 30 April 2014
Accepted 28 May 2014
Available online 2 June 2014

Keywords:
Tolterodine
Hydrogels
Pharamcokinetics
Box-Behnken design
Film-forming

ABSTRACT

A transparent film-forming hydrogel formulation for tolterodine was developed using ternary phase diagram and Box-Behnken design (BBD). Carbopol 980 (neutralized by triethanolamine), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC) and Tween 80 were used as matrices. Solvent was the mixture of water and ethyl alcohol. The measured 24 h cumulative drug release rate (86.02%) was consistent with the predicted value (85.42%) in mice. Steady-state flux (J) of tolterodine in optimized formulation across rat full skin, epidermal, dermis and subcutaneous tissue were 15.83, 18.55, 37.15 and 81.82 $\mu g\,cm^{-2}\,h^{-1}$, respectively. Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) results suggested that the hydrogels could impact lipid status in SC, which was consistent with E_a (8.638 kcal/mol) of tolterodine from optimized formulation in rats. In the pharmacokinetic studies, sustained-release over 24 h and absolute bioavailability of the hydrogels (24.53%) was higher than tolterodine tablets (15.16%) in rats. The hydrogels were suitable for systemic administration of tolterodine for the treatment of overactive bladder.

1. Introduction

Overactive bladder is a common chronic disease that causes much inconvenience in daily life (Abrams and Wein, 1998). Patients primarily use antimuscarinic agents such as tolterodine, oxybutynin, solifenacin and darifenacin for pharmacological treatment of this disease (Abrams et al., 1999; Andersson, 1997). Previously, Ditropan XL (oxybutynin chloride extended release tablets) was the anti-muscarinic drug of choice, but lack of selectivity for the bladder frequently gives rise to bothersome side effects (e.g., dry mouth, constipation, and blurred vision) (Yarker et al., 1995). Against this background, Oxytrol (transdermal oxybutynin) was approved by the Food and Drug Administration (FDA) in 2009. Meanwhile, Detrol LA (tolterodine L-tartrate long-acting capsules) and Detrol (tolterodine tablets) were developed as the first antimuscarinic agents for treatment of overactive bladder. Because of the first-pass effect, oral bioavailability varied over a wide range, resulting in inconsistent therapeutic effects. Due to the scarcity of marketed products, there is a need for a long-acting formulation of tolterodine. Superior to oral formulations, hydrogels are convenient for patients with dysphagia, visible after administration and have fewer side effects due to consistent bioavailability (Deligkaris et al., 2010; Finnin and Morgan, 1999; Lane, 2013).

Tolterodine tartrate and tolterodine free base are sparingly and slightly soluble in water, respectively, making it hard to elevate drug loading in a water-rich matrix upon 2%. For industrial production, preparation of tolterodine free base from the tartrate by extraction is simple, but good quality control is hard to achieve. To solve these problems, mixed gelling agents were used to achieve proper viscosity and gelation in an environment with high concentrations of water and ethyl alcohol. Carbopol 980, hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC) and mixtures of these agents have been used for various medicinal applications (Ito et al., 2007; Michailova et al., 2000). Tween 80 and triethanolamine may further improve matrix properties and increase tolterodine solubility in hydrogels.

Tolterodine hydrogels with film-forming properties were developed to permit administration once a day. Film-forming agents are commonly seen in cosmetics and traditional Chinese medicines, such as protide or resinae (Wang et al., 2010). Gelatin, polyvinyl alcohol (PVA), cellulose derivatives and poly(lactic-co-glycolic acid) (PLGA) can be dissolved in hydrophilic solvents due to their high hydrophilicity (Nagarajan et al., 2013). In this study, hydroxypropyl methyl cellulose (HPMC), frequently used in film-forming and sustained-release products, was chosen as the film-forming agent (Lehr et al., 1992; Zúñiga et al., 2012). It was not

* Corresponding author. Tel.: +86 431 85155320; fax: +86 431 85155320.
E-mail addresses: sunfengying@jlu.edu.cn (F. Sun), liyouxin@jlu.edu.cn (Y. Li).

http://dx.doi.org/10.1016/j.ijpharm.2014.05.051
0378-5173/

sensitive with pH and ion, but transparent after swelling in water and has good compatibility with Carbopol 980.

Response surface methodology (RSM) is a set of mathematical and statistical techniques that can quantify the relationship between measured response variables and explanatory factors, allowing the optimization of response over a series of tests. The main advantage of RSM is the reduced number of experiments needed compared to a full factorial design. The RSM has been widely applied for optimization of pharmaceutical formulations (Hatambeygi et al., 2011). Box-Behnken design (BBD) is a popular form of RSM because it is more effective than other designs and is acknowledged as one of the best statistical and analytical models available (Ghasemi et al., 2011; Zhou et al., 2009).

Fourier transform infrared (FTIR) and differential scanning calorimeter (DSC) are simple and effective ways to evaluate changes of stratum corneum (SC) (Lee et al., 2005; Xiong et al., 1996). Transdermal routes could be investigated by determination of activation energy of drug across skin (Narishetty and Panchagnula, 2004).

Preparation, characterization and pharmacological evaluation of tolterodine hydrogels were reported in our previous study (Sun et al., 2013). The hydrogels were not transparent and without film-forming properties. In the present study, transparent tolterodine hydrogels with film-forming properties were prepared. Drug release rate of tranparent hydrogels would be higher and steadier. Through an RSM design, the formulation was optimized to maximize transdermal drug flux. The hydrogels could impact lipid status in SC, release drug constantly and steadily over 24 h and reach systemic administration of tolterodine for the treatment of overactive bladder.

2. Materials and methods

2.1. Materials

Carbopol 980 was obtained from Anhui Shanhe Pharmaceutical Excipients Co., Ltd. (China). Hydroxypropyl methylcellulose (HPMC), K4 M and hydroxypropyl cellulose (HPC) were purchased from Colorcon, UK. Tolterodine tartrate was purchased from Fuyuan Biotech Co., Ltd. (Tianjin, China). Tolterodine tablets (2 mg × 30) were bought from Lunan Bert Pharmaceuticals Limited (Shandong, China).

All other chemicals were of reagent grade.

Healthy Kunming female mice weighing 20–25 g and healthy Sprague Dawley (S.D.) female rats weighing 180–220 g were supplied by Experimental Animal Center of Jilin University, China. During the experiment, the animals were kept in plastic cages in a room at a temperature of 20 ± 4 °C, with a 12:12 light-dark cycle. They were fed with granulated feed and had free access to water. All experiments were performed according to the Guidelines for Animal Experiments, Jilin University.

2.2. Preparation of tolterodine hydrogels

Tolterodine hydrogels were prepared based on a matrix containing Carbopol 980, HPC, HPMC, Tween 80 and triethanolamine at the concentrations of 1.0% (w/w), 0.5% (w/w), 1.5% (w/w), 1% (w/w), and 2.3% (w/w), respectively. Tolterodine tartrate and triethanolamine were dispersed in the matrix, followed by the addition of ethyl alcohol and water. Weight of the system was 10 g. By varying mixture of tolterodine tartrate and triethanolamine (1:1.59 (w/w)), ethyl alcohol and water composition, about 400 sample points were taken to figure out the compositions which lead to the formation of transparent suspensions, transparent hydrogels and white hydrogels (Fig. 1). Based on the experimentation, the compositions of transparent hydrogels were plotted in a triplot (Fig. 2).

2.3. Preparation of skins

2.3.1. Preparation of full mice skins

Protocols for all animal experiments were performed according to the Guidelines for Animal Experiments, Jilin University. Female mice (body weight 20–25 g) were treated with 7% (w/w) Na_2S solution to dislodge hair from the ventral skin. Briefly, hair was wetted with the solution for approximately 5 min until mud-like and then scraped off with a blade. Subcutaneous fat was carefully removed from the dermal surface with scalpel and washed with saline solution. The skin was washed 3 times with deionized water

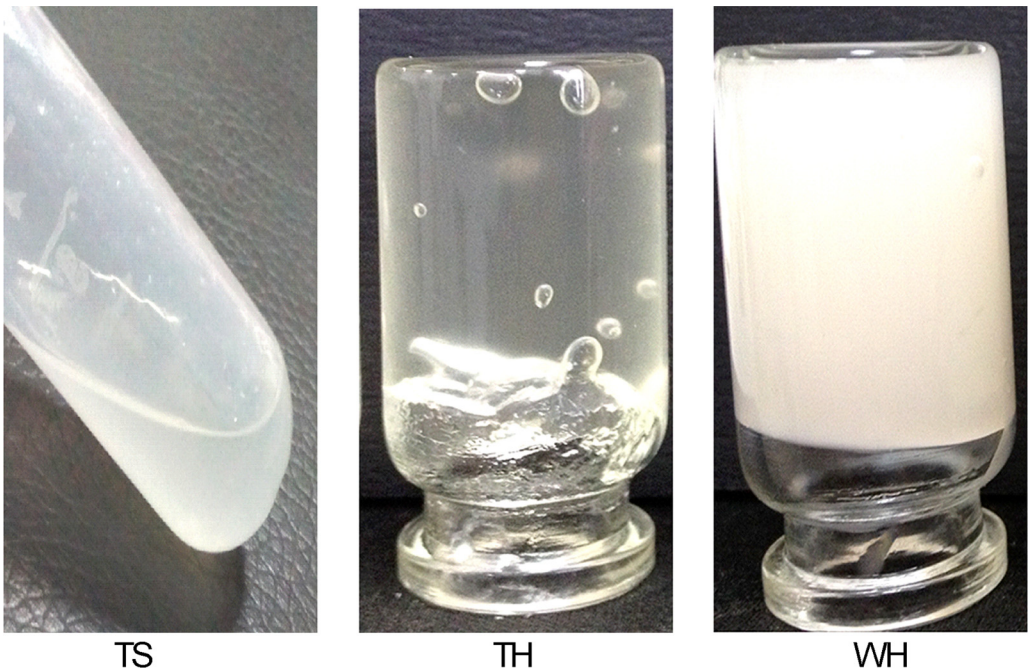

Fig. 1. Morphological observations of transparent suspensions (TS), transparent hydrogels (TH), white hydrogels (WH).